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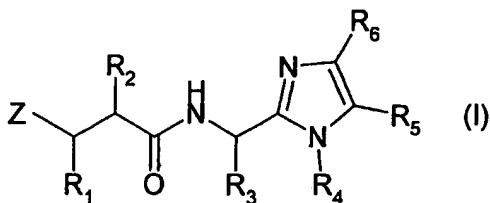
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**WO 02/41886 A1**

**(54) Title: YDROXAMIC ACID OR N-FORMYL HYDROXYLAMINE DERIVATIVES AS INHIBITORS OF BAKTERIAL POLYPEPTIDE DEFORMYLASE FOR TREATING MICROBIAL INFECTIONS**



in the specification.

**(57) Abstract:** Compounds of formula (I) are antibacterial or antiprotozoal agents for treatment of infections in humans and non-human mammals, wherein: Z represents a radical of formula -N(OH)CH(=O) or formula C(=O)NH(OH); R<sub>1</sub> represents hydrogen, methyl or trifluoromethyl, or except when Z is a radical of formula -N(OH)CH(=O), a hydroxy, halo or amino group; R<sub>2</sub> represents a group R<sub>10</sub>-(X)<sub>n</sub>-(ALK)<sub>m</sub> wherein R<sub>10</sub>, ALK, X, m and n are as defined in the specification; R<sup>3</sup> represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl or phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl-; and R<sub>5</sub> and R<sub>6</sub> are as defined

## HYDROXAMIC ACID OR N-FORMYL HYDROXYLAMINE DERIVATIVES AS INHIBITORS OF BACTERIAL POLYPEPTIDE DEFORMYLASE FOR TREATING MICROBIAL INFECTIONS

This invention relates to the use of hydroxamic acid and N-formyl hydroxylamine derivatives as antibacterial and antiprotozoal agents, to novel compounds within those classes, and to pharmaceutical and veterinary compositions comprising such compounds.

Background to the Invention

In general, bacterial pathogens are classified as either Gram-positive or Gram-negative. Many antibacterial agents (including antibiotics) are specific against one or other Gram-class of pathogens. Antibacterial agents effective against both Gram-positive and Gram-negative pathogens are therefore generally regarded as having broad spectrum activity.

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes.

Amongst the Gram-positive pathogens, such as Staphylococci, Streptococci, Mycobacteria and Enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin, quinolone or macrolide resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*.

Pathogenic bacteria are often resistant to the aminoglycoside,  $\beta$ -lactam (penicillins and cephalosporins), macrolide, quinolone and chloramphenicol types of antibiotic. The mechanism of resistance can involve the enzymatic inactivation of the antibiotic by hydrolysis, formation of inactive derivatives, mutation of the molecular target and/or activation of transport pumps. The  $\beta$ -lactam (penicillin and cephalosporin) family of antibiotics are characterised by the presence of a  $\beta$ -lactam ring structure. Resistance to this family of antibiotics in clinical isolates is most commonly due to the production of a "penicillinase" ( $\beta$ -lactamase) enzyme by the resistant bacterium which hydrolyses the  $\beta$ -lactam ring thus eliminating its antibacterial activity.

Recently there has been an emergence of vancomycin-resistant strains of enterococci (Woodford N. 1998 Glycopeptide-resistant enterococci: a decade of experience. Journal of Medical Microbiology. 47(10):849-62). Vancomycin-resistant enterococci are particularly hazardous in that they are frequent causes of hospital based infections and are inherently resistant to most antibiotics. Vancomycin works by binding to the terminal D-Ala-D-Ala residues of the cell wall peptidoglycan precursor. The high-level resistance to vancomycin is known as VanA and is conferred by genes located on a transposable element which alter the terminal residues to D-Ala-D-lac thus reducing the affinity for vancomycin.

In view of the rapid emergence of multidrug-resistant bacteria, the development of antibacterial agents with novel modes of action that are effective against the growing number of resistant bacteria, particularly the vancomycin resistant enterococci and  $\beta$ -lactam antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, is of utmost importance.

#### Brief Description of the Invention

This invention is based on the finding that certain hydroxamic acid and N-formyl hydroxylamine derivatives having imidazole substituents have antibacterial and antiprotozoal activity, and makes available new antibacterial and antiprotozoal agents. The compounds with which this invention is

concerned are antibacterial with respect to a range of Gram-positive and Gram-negative organisms.

Although it may be of interest to establish the mechanism of action of the compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

All ribosome-mediated synthesis of proteins starts with a methionine residue. In prokaryotes, the methionyl moiety carried by the initiator tRNA is N-formylated prior to its incorporation into a polypeptide. Consequently, N-formylmethionine is always present at the N-terminus of a nascent bacterial polypeptide. However, most mature proteins do not retain the N-formyl group or the terminal methionine residue. Deformylation is required prior to methionine removal, since methionine aminopeptidase does not recognise peptides with an N-terminal formylmethionine residue (Solbiati et al., J. Mol. Biol. 290:607-614, 1999). Deformylation is, therefore, a crucial step in bacterial protein biosynthesis and the enzyme responsible, PDF, is essential for normal bacterial growth. Although the gene encoding PDF (*def*) is present in all pathogenic bacteria for which sequences are known (Meinzel et al., J. Mol. Biol. 266:939-49, 1997), it has no known eukaryotic counterpart, making it an attractive target for antibacterial chemotherapy (for a review see Giglione et al., Mol Microbiol., 36: 1197-1205, 2000).

The isolation and characterisation of PDF has been facilitated by an understanding of the importance of the metal ion in the active site (Groche et al., Biophys. Biochem. Res. Commun., 246:324-6, 1998). The Fe<sup>2+</sup> form is highly active *in vivo* but is unstable when isolated due to oxidative degradation (Rajagopalan et al., J. Biol. Chem. 273:22305-10, 1998). The Ni<sup>2+</sup> form of the enzyme has specific activity comparable with the ferrous enzyme but is oxygen-insensitive (Ragusa et al., J. Mol. Biol. 1998, 280:515-23, 1998). The

Zn<sup>2+</sup> enzyme is also stable but is almost devoid of catalytic activity (Rajagopalan et al., J. Am. Chem. Soc. 119:12418-12419, 1997).

Several X-ray crystal structures and NMR structures of *E. coli* PDF, with or without bound inhibitors, have been published (Chan et al., Biochemistry 36:13904-9, 1997; Becker et al., Nature Struct. Biol. 5:1053-8, 1998; Becker et al., J. Biol. Chem. 273:11413-6, 1998; Hao et al., Biochemistry, 38:4712-9, 1999; Dardel et al., J. Mol. Biol. 280:501-13, 1998; O'Connell et al., J. Biomol. NMR, 13:311-24, 1999), indicating similarities in active site geometry to metalloproteinases such as thermolysin and the metzincins.

The substrate specificity of PDF has been extensively studied (Ragusa et al., J. Mol. Biol. 289:1445-57, 1999; Hu et al., Biochemistry 38:643-50, 1999; Meinnel et al., Biochemistry, 38:4287-95, 1999). These authors conclude that an unbranched hydrophobic chain is preferred at P1', while a wide variety of P2' substituents are acceptable and an aromatic amide substituent may be advantageous at the P3' position. There have also been reports that small peptidic compounds containing an H-phosphonate (Hu et al., Bioorg. Med. Chem. Lett., 8:2479-82, 1998) or thiol (Meinnel et al., Biochemistry, 38:4287-95, 1999; Huntingdon et al., Biochemistry, 39: 4543-51, 2000; Wei et al., J. Combinatorial Chem., 2: 650-57, 2000) metal binding group are micromolar inhibitors of PDF. Peptide aldehydes such as calpeptin (N-Cbz-Leu-norleucinal) have also been shown to inhibit PDF (Durand et al., Arch. Biochem. Biophys., 367:297-302, 1999). Recently, the naturally occurring hydroxamic acid antibiotic actinonin, for which the target of its antibacterial activity was previously unknown, was shown to be a potent inhibitor of polypeptide deformylase (WO 99/39704, and Chen et al, Biochemistry, 39: 1256-62, 2000). Examples of non-peptidic PDF inhibitors with a carboxylic acid (Green et al., Arch. Biochem. Biophys. 375: 355-8, 2000; Jayasekera et al., ibid., 381:313-6, 2000) or hydroxamic acid (Apfel et al., J. Med. Chem., 43: 2324-31, 2000) metal binding groups are also known.

It has been reported that PDF is present in eukaryotic parasites such as *Plasmodium falciparum* (Meinzel, Parasitology Today, 16: 165-8, 2000). Those authors also found evidence for the presence of PDF in other parasites of humans, such as the kinetoplastid protozoan parasites *Trypanosoma brucei* and *Leishmania major*. Based on these findings, it is anticipated that the hydroxamic acid and N-formyl hydroxylamine compounds with which this invention is concerned have antiprotozoal activity, and are useful in the treatment of malaria and other protozoal diseases.

Certain N-formyl hydroxylamine derivatives have previously been claimed in the patent publications listed below, although very few examples of such compounds have been specifically made and described:

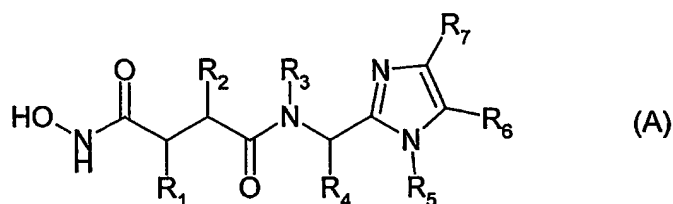
|              |                          |
|--------------|--------------------------|
| EP-B-0236872 | (Roche)                  |
| WO 92/09563  | (Glycomed)               |
| WO 92/04735  | (Syntex)                 |
| WO 95/19965  | (Glycomed)               |
| WO 95/22966  | (Sanofi Winthrop)        |
| WO 95/33709  | (Roche)                  |
| WO 96/23791  | (Syntex)                 |
| WO 96/16027  | (Syntex/Agouron)         |
| WO 97/03783  | (British Biotech)        |
| WO 97/18207  | (DuPont Merck)           |
| WO 98/38179  | (Glaxo-Wellcome)         |
| WO 98/47863  | (Labs Jaques Logeais)    |
| WO 99/06361  | (Abbott Laboratories)    |
| WO 00/12082  | (Glaxo-Wellcome)         |
| WO 00/12083  | (Glaxo-Wellcome)         |
| WO 00/12466  | (Glaxo-Wellcome)         |
| WO 00/12478  | (Zeneca)                 |
| WO 00/44712  | (Abbott Laboratories)    |
| WO 00/44739  | (Abbott Laboratories)    |
| WO 00/59285  | (DuPont Pharmaceuticals) |

The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis.

In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives, however, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) and a recent publication (Robl et al., Bioorg. Med. Chem. Lett., 10: 257-60, 2000) disclose certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors.

Patent publications WO 99/41232 (British Biotech) and WO 00/43001 (British Biotech) respectively disclose the use of certain N-formyl hydroxylamine derivatives as inhibitors of proliferation of rapidly dividing cells and in the treatment of inflammation.

Very many hydroxamic acid derivatives are known. Many have been disclosed as having matrix metalloproteinase (MMP) inhibitory activity, and thus to be potentially useful for the treatment of diseases mediated by MMPs, for example cancer, arthritides, and conditions involving tissue remodeling such as wound healing, and restenosis. WO 95/23790 (SmithKline Beecham) discloses MMP and cytokine inhibiting hydroxamic acid derivatives of formula (A)

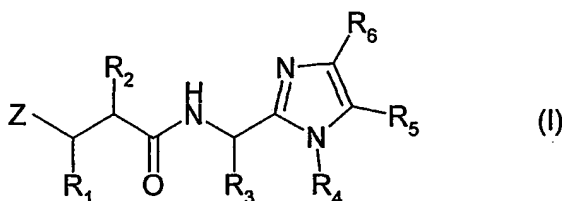


wherein the variable R groups are as defined in the specification. Similar compounds have been disclosed in WO 96/33176 (DuPont Merck) and in Chen et. al., Bioorg. Med. Chem. Lett., 1996, 6, 1601-1606, as inhibitors of MMPs and inhibitors of Tumour Necrosis Factor production. Neither of these publications suggest that compounds (A) have antibacterial or antiprotozoal activity.

Our copending International patent applications nos. WO 99/39704, WO 99/59568, WO 00/35440, WO 00/44373, WO 00/58294 and WO 00/61134 disclose that certain N-formyl hydroxylamine and hydroxamic acid derivatives have antibacterial activity.

#### Detailed description of the invention

According to the first aspect of the present invention there is provided the use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof in the preparation of a composition for treatment of bacterial or protozoal infections in humans and non-human mammals:



wherein:

Z represents a radical of formula  $-N(OH)CH(=O)$  or formula  $-C(=O)NH(OH)$ ;

$R_1$  represents hydrogen, methyl or trifluoromethyl, or, except when Z is a radical of formula  $-N(OH)CH(=O)$ , a hydroxy, halo or amino group;

$R_2$  represents a group  $R_{10}-(X)_n-(ALK)_m$  wherein



R<sub>10</sub> represents hydrogen, or a C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, cycloalkyl, aryl, or heterocyclyl group, any of which may be unsubstituted or substituted by (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo, -COOH, -CONH<sub>2</sub>, -COOR<sup>A</sup>, -NHCOR<sup>A</sup>, -CONHR<sup>A</sup>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, or -CONR<sup>A</sup>R<sup>B</sup> wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>)alkyl group and

ALK represents a straight or branched divalent C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>2</sub>-C<sub>6</sub> alkenylene, or C<sub>2</sub>-C<sub>6</sub> alkynylene radical, and may be interrupted by one or more non-adjacent -NH-, -O- or -S- linkages,

X represents -NH-, -O- or -S-, and

m and n are independently 0 or 1;

R<sub>3</sub> represents the side chain of a natural or non-natural alpha amino acid; and

R<sub>4</sub> represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl or phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl-; and

(a) R<sub>5</sub> and R<sub>6</sub> independently represent:

hydrogen, halogen, trifluoromethyl, or

(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, aryl, heterocyclyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl-, or heterocyclyl(C<sub>1</sub>-C<sub>6</sub>)alkyl-, any of which may be optionally substituted by

(C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, trifluoromethyl, cyano, nitro, oxo,

phenoxy or phenylthio-,

-OR<sup>A</sup>, -SR<sup>A</sup>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, -NHCOR<sup>A</sup>, -CONHR<sup>A</sup>, -CONR<sup>A</sup>R<sup>B</sup>,  
or -COOR<sup>A</sup>, wherein

R<sup>A</sup> and R<sup>B</sup> are independently hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl,

or in the case where R<sup>A</sup> and R<sup>B</sup> are attached to a nitrogen atom then R<sup>A</sup> and R<sup>B</sup> taken together with the nitrogen atom to which they are attached form a monocyclic 5-7 membered ring; or

- (b) R<sub>5</sub> and R<sub>6</sub> taken together with the carbon atoms to which they are attached form a fused monocyclic or bicyclic carbocyclic or heterocyclic ring which may be further substituted with any of the substituent groups listed under (a).

In another aspect, the invention provides a method for the treatment of bacterial or protozoal infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially or antiprotozoally effective dose of a compound of formula (I) as defined above.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound of formula (I) as defined above to the site of contamination.

The compounds of formula (I) as defined above may be used as component(s) of antibacterial cleaning or disinfecting materials.

Compounds of formula (I) above wherein Z is a radical of formula -N(OH)CH(=O), are believed to be novel. Accordingly, in another aspect, the invention provides a compound of formula (I) wherein Z is a radical of formula -N(OH)CH(=O), or a pharmaceutically or veterinarily acceptable salt, hydrate

or solvate thereof. Furthermore, to the extent that compounds of formula (I) above wherein Z is a radical of formula  $-C(=O)NH(OH)$  do not form part of the state of the art, such compounds and their pharmaceutically or veterinarily acceptable salts, hydrates or solvates are also an aspect of the present invention.

On the hypothesis that the compounds (I) act by inhibition of intracellular PDF, the most potent antibacterial effect may be achieved by using compounds which efficiently pass through the bacterial cell wall. Thus, compounds which are highly active as inhibitors of PDF in vitro and which penetrate bacterial cells are preferred for use in accordance with the invention. It is to be expected that the antibacterial potency of compounds which are potent inhibitors of the PDF enzyme in vitro, but are poorly cell penetrant, may be improved by their use in the form of a prodrug, ie a structurally modified analogue which is converted to the parent molecule of formula (I), for example by enzymic action, after it has passed through the bacterial cell wall. The same is true in the case of protozoa.

As used herein the term "(C<sub>1</sub>-C<sub>6</sub>)alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C<sub>1</sub>-C<sub>6</sub>)alkylene radical" means a saturated hydrocarbon chain having from 1 to 6 carbon atoms and two unsatisfied valencies.

As used herein the term "(C<sub>2</sub>-C<sub>6</sub>)alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "divalent (C<sub>2</sub>-C<sub>6</sub>)alkenylene radical" means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one double bond, and two unsatisfied valencies.

As used herein the term "C<sub>2</sub>-C<sub>6</sub> alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "divalent (C<sub>2</sub>-C<sub>6</sub>)alkynylene radical" means a hydrocarbon chain having from 2 to 6 carbon atoms, at least one triple bond, and two unsatisfied valencies.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "cycloalkenyl" means an unsaturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic group, and to groups consisting of two covalently linked monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and naphthyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined below, and in particular means a 5-8 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzyl or

second heterocyclic ring, and the term includes, for example, pyrrolyl, furyl, thienyl, piperidinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thiazepinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, and benzimidazolyl rings.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring containing one or more heteroatoms, and optionally fused to a benzyl or pyridyl ring; and to groups consisting of two covalently linked 5- or 6- membered aromatic rings each containing one or more heteroatoms; and to groups consisting of a monocyclic carbocyclic aromatic group covalently linked to a 5- or 6- membered aromatic rings containing one or more heteroatoms. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, 4-([1,2,3]-thiadiazol-4-yl)phenyl and 5-isoxazol-3-ylthienyl.

As used herein the unqualified term "carbocyclyl" or "carbocyclic" refers to a 5-8 membered ring whose ring atoms are all carbon.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl, benzyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, phenoxy, hydroxy, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo, -COOH, -CONH<sub>2</sub>, -COR<sup>A</sup>, -COOR<sup>A</sup>, -NHCOR<sup>A</sup>, -CONHR<sup>A</sup>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, or -CONR<sup>A</sup>R<sup>B</sup> wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>)alkyl group. In the case where "substituted" means substituted by benzyl, the phenyl ring thereof may itself be substituted with any of the foregoing, except phenyl or benzyl.

As used herein the terms "side chain of a natural alpha-amino acid" and "side chain of a non-natural alpha-amino acid" mean the group R<sup>x</sup> in respectively a natural and non-natural amino acid of formula NH<sub>2</sub>-CH(R<sup>x</sup>)-COOH.

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine,  $\alpha$ -aminoadipic acid,  $\alpha$ -amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine,  $\alpha$ -methylserine, ornithine, pipecolic acid, and thyroxine.

In natural alpha-amino acid side chains which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups as in arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine, such functional substituents may optionally be protected.

Likewise, in the side chains of non-natural alpha amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups, such functional substituents may optionally be protected.

The term "protected" when used in relation to a functional substituent in a side chain of a natural or non-natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. The widely used handbook by T. W. Greene and P. G. Wuts "Protective Groups in Organic Synthesis" Second Edition, Wiley, New York, 1991 reviews the subject. For example, carboxyl groups may be esterified (for example as a C<sub>1</sub>-C<sub>6</sub> alkyl ester), amino groups may be converted to amides (for example as a NHCOC<sub>1</sub>-C<sub>6</sub> alkyl amide) or carbamates (for example as an NHC(=O)OC<sub>1</sub>-C<sub>6</sub> alkyl or NHC(=O)OCH<sub>2</sub>Ph carbamate), hydroxyl groups may be converted to ethers (for example an OC<sub>1</sub>-C<sub>6</sub> alkyl or a O(C<sub>1</sub>-C<sub>6</sub> alkyl)phenyl ether) or esters (for example a OC(=O)C<sub>1</sub>-C<sub>6</sub> alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a SC(=O)C<sub>1</sub>-C<sub>6</sub> alkyl thioester).

There are at least two actual or potential chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereoconfiguration of the carbon atom carrying the R<sub>2</sub> group is R; that of the carbon atom carrying the R<sub>1</sub> group (when asymmetric) is R; and that of the carbon atom carrying the R<sub>3</sub> group (when asymmetric) is S

In the compounds of formula (I) as defined above:

When Z is a radical of formula -N(OH)CH(=O) R<sub>1</sub> is hydrogen, methyl or trifluoromethyl. When Z is a radical of formula -C(=O)NH(OH) R<sub>1</sub> is hydrogen, methyl, trifluoromethyl, hydroxy, halo (e.g. chloro, bromo or especially fluoro) or amino. Hydrogen is currently preferred in both cases.

R<sub>2</sub> may be, for example:

optionally substituted C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> alkynyl or cycloalkyl;

phenyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, phenyl(C<sub>3</sub>-C<sub>6</sub> alkenyl)- or phenyl(C<sub>3</sub>-C<sub>6</sub> alkynyl)- optionally substituted in the phenyl ring;

cycloalkyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, cycloalkyl(C<sub>3</sub>-C<sub>6</sub> alkenyl)- or cycloalkyl(C<sub>3</sub>-C<sub>6</sub> alkynyl)- optionally substituted in the cycloalkyl ring;

heterocyclyl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, heterocyclyl(C<sub>3</sub>-C<sub>6</sub> alkenyl)- or heterocyclyl(C<sub>3</sub>-C<sub>6</sub> alkynyl)- optionally substituted in the heterocyclyl ring; or

CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>O(CH<sub>2</sub>)<sub>q</sub>- or CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>S(CH<sub>2</sub>)<sub>q</sub>-, wherein p is 0, 1, 2 or 3 and q is 1, 2 or 3.

Specific examples of R<sub>2</sub> groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at R<sub>2</sub> are n-propyl, n-butyl, n-pentyl, and cyclopentylmethyl.

R<sub>3</sub> may be, for example

the characterising group of a natural  $\alpha$ -amino acid, for example benzyl, or 4-hydroxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group -[Alk]<sub>n</sub>R<sub>9</sub> where Alk is a (C<sub>1</sub>-C<sub>6</sub>)alkylene or (C<sub>2</sub>-C<sub>6</sub>)alkenylene group optionally interrupted by one or more -O-, or -S- atoms or -N(R<sub>12</sub>)- groups [where R<sub>12</sub> is a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group], n is 0 or 1, and R<sub>9</sub> is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when n is 1) R<sub>9</sub> may additionally be hydroxy, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, -CONH<sub>2</sub>, -COOR<sup>A</sup>, -NHCOR<sup>A</sup>, -CONHR<sup>A</sup>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, or -CONR<sup>A</sup>R<sup>B</sup> wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; or



a benzyl group substituted in the phenyl ring by a group of formula -OCH<sub>2</sub>COR<sub>8</sub> where R<sub>8</sub> is hydroxyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, di((C<sub>1</sub>-C<sub>6</sub>)alkyl)amino, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkylamino; or

a heterocyclic(C<sub>1</sub>-C<sub>6</sub>)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, trifluoromethyl (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy, formyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, di-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, mercapto(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkylphenylmethyl; or

a group -CR<sub>a</sub>R<sub>b</sub>R<sub>c</sub> in which:

each of R<sub>a</sub>, R<sub>b</sub> and R<sub>c</sub> is independently hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl; or

R<sub>c</sub> is hydrogen and R<sub>a</sub> and R<sub>b</sub> are independently phenyl or heteroaryl such as pyridyl; or

R<sub>c</sub> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, or (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, and R<sub>a</sub> and R<sub>b</sub> together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R<sub>a</sub>, R<sub>b</sub> and R<sub>c</sub> together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R<sub>a</sub> and R<sub>b</sub> are each independently (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, or a group as defined for R<sub>c</sub> below other than hydrogen, or R<sub>a</sub> and R<sub>b</sub> together with the carbon atom to which they are attached form a cycloalkyl or

heterocyclic ring, and  $R_c$  is hydrogen, -OH, -SH, halogen, -CN, -CO<sub>2</sub>H, (C<sub>1</sub>-C<sub>4</sub>)perfluoroalkyl, -CH<sub>2</sub>OH, -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -O(C<sub>1</sub>-C<sub>6</sub>)alkyl, -O(C<sub>2</sub>-C<sub>6</sub>)alkenyl, -S(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -S(C<sub>2</sub>-C<sub>6</sub>)alkenyl, -SO(C<sub>2</sub>-C<sub>6</sub>)alkenyl, -SO<sub>2</sub>(C<sub>2</sub>-C<sub>6</sub>)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO<sub>2</sub>- and W represents a phenyl, phenylalkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylalkyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO<sub>2</sub>H, -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1</sub>-C<sub>6</sub>)alkyl, -CONH(C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>, -CHO, -CH<sub>2</sub>OH, (C<sub>1</sub>-C<sub>4</sub>)perfluoroalkyl, -O(C<sub>1</sub>-C<sub>6</sub>)alkyl, -S(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub>)alkyl, -N((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>, -NHCO(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenyl, phenyl or benzyl.

Examples of particular  $R_3$  groups include methyl, ethyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxyethyl, 2-carboxyethyl, 2-methylcarbamoyl, 2-carbamoyl, and 4-aminobutyl. Presently preferred  $R_3$  groups include tert-butyl.

$R_4$  may be, for example, hydrogen, methyl or ethyl.

$R_5$  and  $R_6$  may independently be, for example, hydrogen, methyl, trifluoromethyl, phenyl, bromo, chloro, fluoro, methoxy, hydroxymethyl, dimethylaminomethyl-, ethoxymethyl-, 4-methyl-piperazine-1-carbonyl-, 4-methyl-piperazin-1-ylmethyl-, morpholin-4-ylmethyl-, methoxycarbonyl, thiazol-2-yl-, phenoxymethyl-, pyrrolidin-1-ylmethyl-, piperidin-1-ylmethyl-, -C(O)NH<sub>2</sub>,

(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CH(OH)CH(CH<sub>3</sub>)<sub>2</sub>, -CH(OH)CH<sub>3</sub>, -CH(OH)Ph, or R<sub>5</sub> and R<sub>6</sub> taken together with the carbon atoms to which they are attached may form a fused benzo, naphtho or pyrido, for example a [4,5-c]pyridin-2-yl, ring, which may be substituted as specified, for example a fused benzo ring substituted by methyl, cyano, hydroxy, chloro or fluoro in the 4- or 5-position.

Specific examples of compounds within or for use within the scope of the invention include the following N-formyl hydroxylamine derivatives, and their corresponding hydroxamic acid analogues:

*2R*-Cyclopentylmethyl-*N*-[1*S*-(5-fluoro-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-3-(formyl-hydroxy-amino)-propionamide;

*N*-[1-(5-Chloro-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide;

*N*-[1-(1*H*-Benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide;

2-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1-(1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-amide;

3-Cyclopentyl-*N*-[1*S*-(6-dimethylaminomethyl-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-*N*-[1*S*-(6-dimethylaminomethyl-1-methyl-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

*N*-(1*S*-{6-[(Acetyl-methyl-amino)-methyl]-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl)-3-cyclopentyl-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-2*R*-[(formyl-hydroxy-amino)-methyl]-*N*-[1*S*-(6-hydroxymethyl-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-propionamide;

3-Cyclopentyl-*N*-[1*S*-(5-dimethylaminomethyl-1*H*-imidazol-2-yl)-2,2-dimethyl-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-*N*-[1*S*-(6-ethoxymethyl-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-*N*-[1*S*-(5-ethoxymethyl-1*H*-imidazol-2-yl)-2,2-dimethyl-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

*N*-[1*S*-(5-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-methyl)-1*H*-imidazol-2-yl)-2,2-dimethyl-propyl]-3-cyclopentyl-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-2*R*-[(formyl-hydroxy-amino)-methyl]-*N*-[1*S*-(1*H*-imidazo[4,5-*c*]pyridin-2-yl)-2,2-dimethyl-propyl]-propionamide;

3-Cyclopentyl-*N*-[1*S*-(1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-2,2-dimethyl-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-*N*-{2,2-dimethyl-1*S*-[5-(4-methyl-piperazine-1-carbonyl)-1*H*-imidazol-2-yl]-propyl}-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-*N*-{2,2-dimethyl-1*S*-[5-(4-methyl-piperazin-1-ylmethyl)-1*H*-imidazol-2-yl]-propyl}-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-*N*-[2,2-dimethyl-1*S*-(5-morpholin-4-ylmethyl-1*H*-imidazol-2-yl)-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-2*R*-[(formyl-hydroxy-amino)-methyl]-*N*-[1*S*-(1*H*-imidazol-2-yl)-2,2-dimethyl-propyl]-propionamide;

2-(1*S*-(3-Cyclopentyl-2*R*-[(formyl-hydroxy-amino)-methyl]-propionylamino)-2,2-dimethyl-propyl)-3*H*-imidazole-4-carboxylic acid methyl ester;

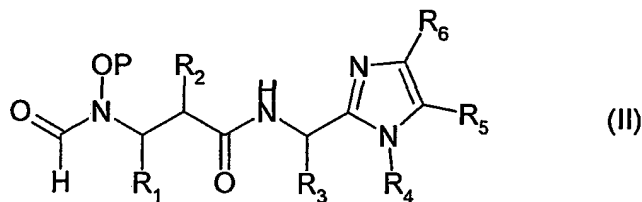
3-Cyclopentyl-*N*-[2,2-dimethyl-1*S*-(5-thiazol-2-yl-1*H*-imidazol-2-yl)-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

3-Cyclopentyl-*N*-[2,2-dimethyl-1*S*-(5-phenoxy-methyl-1*H*-imidazol-2-yl)-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide;

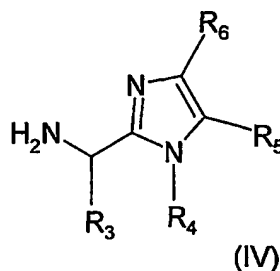
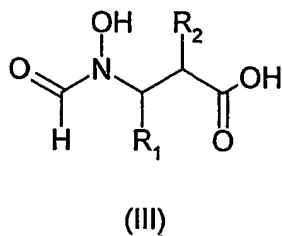
3-Cyclopentyl-*N*-[2,2-dimethyl-1*S*-(5-pyrrolidin-1-ylmethyl-1*H*-imidazol-2-yl)-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide; and

3-Cyclopentyl-*N*-[2,2-dimethyl-1*S*-(5-piperidin-1-ylmethyl-1*H*-imidazol-2-yl)-propyl]-2*R*-[(formyl-hydroxy-amino)-methyl]-propionamide.

Compounds of the invention wherein Z is a radical of formula -N(OH)CH(=O) may be prepared by deprotection of a compound of formula (II)

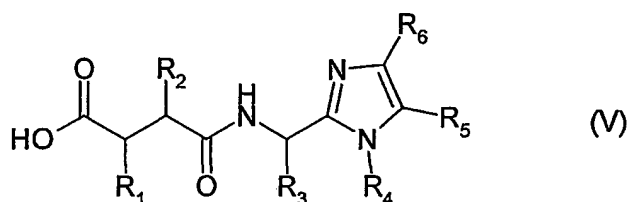


wherein P represents a hydroxy protecting group, and  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are as defined in relation to formula (II). Compounds of formula (II) may be prepared by coupling a carboxylic acid of formula (III),

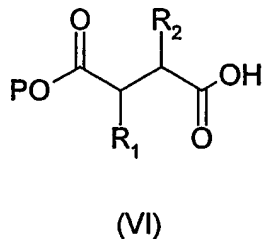


with an amine of formula (IV) using standard peptide coupling methods. Carboxylic acids of formula (III) may be prepared by analogy with the methods described in WO 99/39704. Amines of formula (IV) may be prepared according to any of a variety of methods described in the literature (Chen et al., Bioorg. Med. Chem. Lett., 1996, 6, 1601-1606; Gordon et al., Tetrahedron Lett. 34, 1901-1904, 1993; Gordon et al., Bioorg. Med. Chem. Lett., 1993, 3, 915-920; Abdel-Meguid et al., Biochemistry 33: 11671-7, 1994) and in (WO 93/02057, 95/23790 and WO 96/33176).

Hydroxamate compounds of formula (I) for use in accordance with the invention may be prepared by reacting a compound of formula (V) or a carboxyl-activated derivative thereof



with hydroxylamine or an N- and/or O-protected hydroxylamine, and thereafter removing any O- or N-protecting groups. Carboxyl-activated derivatives of compound (V) include 1-hydroxybenzotriazole ester and pentafluorophenyl ester. A compound of formula (V) may be prepared by standard peptide coupling methods from a carboxylic acid of formula (VI), wherein P is as defined in relation to formula (II), and an amine of formula (IV), followed by removal of P.



Compounds of formula (VI) are well known starting materials in the synthesis of matrix metalloproteinase inhibitors.

Antibacterial or antiprotozoal compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the active ingredient(s) may be made up into a cream, lotion or ointment. Cream or ointment formulations which may

be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceuticals such as the British Pharmacopoeia.

The active ingredient(s) may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. Intra-venous infusion is another route of administration for the compounds used in accordance with the invention.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate embodiments of the invention.  $^1\text{H}$  and spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 MHz. Mass spectra were obtained using a Perkin Elmer Sciex API 165 spectrometer using both positive and negative ionisation modes. Analytical HPLC was performed on a Beckman System Gold, using Waters Nova Pak C18 column (150 mm, 3.9 mm) with 20 to 90 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 0.05% TFA in 10% water 90% methanol; Solvent B: 0.05% TFA in 10% methanol 90%], detection wavelength at 214 nm. Preparative HPLC was performed on a Gilson autoprep instrument using a C18 Waters delta prep-pak cartridge (15 $\mu\text{m}$ , 300 A, 25 mm, 10 mm) with 20 to 90 % solvent B gradient (6 ml/min) as the mobile phase. [Solvent A water; Solvent B: methanol], UV detection was at 214 nm.

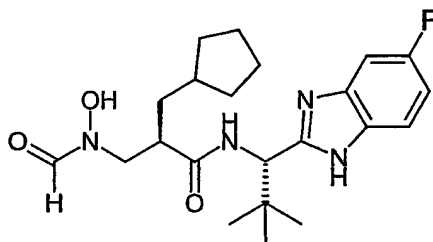
The following abbreviations have been used throughout:



|      |                                                              |
|------|--------------------------------------------------------------|
| EDC  | N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride |
| HPLC | High performance liquid chromatography                       |
| LRMS | Low resolution mass spectrometry                             |
| NMR  | Nuclear magnetic resonance                                   |
| RT   | Retention Time                                               |

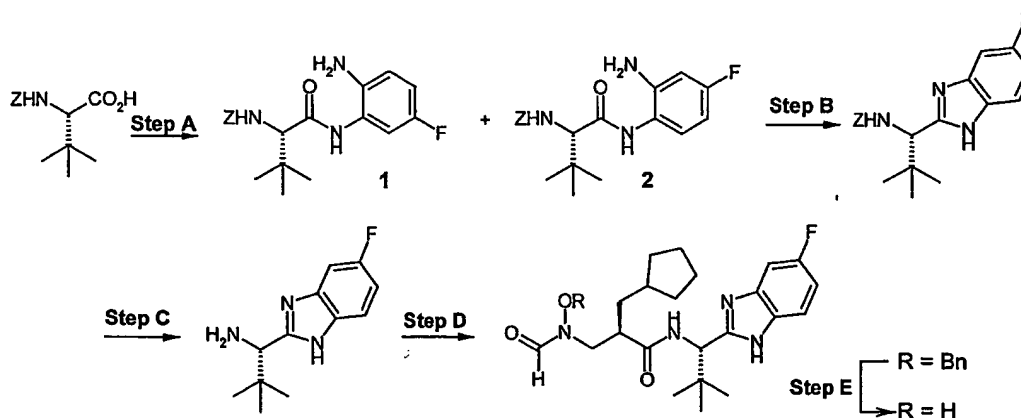
## Example 1

2*R*-Cyclopentylmethyl-*N*-[1*S*-(5-fluoro-1*H*-benzimidazol-2-yl)-2,2-dimethylpropyl]-3-(formyl-hydroxy-amino)-propionamide



The title compound was prepared as outlined in Scheme 1 and is described in detail below.

## Scheme 1



Step A: 5-fluoro 1,2-diamino benzene, EDC,  $\text{CH}_2\text{Cl}_2$ ; Step B: AcOH, 65 C, 12 hrs; Step C: AcOH/HBr 48%, 4 hrs; Step D: 4-benzyloxy-2*R*-cyclopentylmethyl-4-formylamino-butyric acid pentafluorophenylester,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; Step E:  $\text{H}_2$ , Pd/C, EtOH, 30 min

## Step A:

Compound 1: [1S-(2-Amino-5-fluoro-phenylcarbamoyl)-2,2-dimethyl-propyl]-carbamic acid benzyl ester

Compound 2: [1S-(2-Amino-4-fluoro-phenylcarbamoyl)-2,2-dimethyl-propyl]-carbamic acid benzyl ester

To a solution of *Z-tert*-leucine (4.04 g, 1.54 mmol) in dichloromethane (15 ml), was added the 1,2-diamine (2.57 g, 1.68 mmol) followed by EDC (3.21g, 1.68 mmol). The resulting reaction mixture was stirred at room temperature for 12 hrs. The reaction mixture was then diluted with dichloromethane and washed with water (30 ml), 1M aq. Na<sub>2</sub>CO<sub>3</sub> (30 ml), 1M HCl (20 ml) and brine. The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and the solvent was removed *in vacuo* to yield a pale yellow foam which was purified by flash chromatography (hexane:ethyl acetate, 3:1) to give a mixture of regioisomeric compounds, 1 and 2. A further purification by flash chromatography afforded compound 1 as a pure solid (2.44g, 43% yield). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>, mixture of 1 and 2), 7.71 (1H, br s), 7.38-7.27 (5H, m), 7.04-6.98 (1H, m), 6.44-6.36 (2H, m), 5.63 (1H, br d), 5.13-4.99 (2H, AB system), 4.16-4.08 (1H, m), 3.94 (2H, br s), 1.09 (9H, s).

(N.B. Both 1 and 2 give the same compound after cyclisation.)

Step B: [1S-(5-Fluoro-1*H*-benzimidazol-2-yl)-2,2-dimethyl-propyl]-carbamic acid benzyl ester

A solution of the mixture of 1 and 2 (2.24 g, 6.45 mmol) in glacial acetic acid (25 ml) was heated to 65°C for 12 hrs. Acetic acid was removed under reduced pressure. The resulting salt was partitioned between dichloromethane and 1M aq. Na<sub>2</sub>CO<sub>3</sub>. The organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The resulting crude reaction mixture was purified by flash chromatography (hexane / ethyl acetate: 3/1) to give the title compound

(1.92 g, 84% yield). LRMS: +ve ion 356 [M+1], -ve ion 354 [M-1]; HPLC data: RT 5.13 min.

**Step C: 1S-(6-Fluoro-1H-benzoimidazol-2-yl)-2,2-dimethyl-propylamine**

To a cold (5°C) solution of [1S-(5-fluoro-1H-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-carbamic acid benzyl ester (400 mg, 1.13 mmol) in acetic acid (10 ml) was added 48% HBr in H<sub>2</sub>O (12 ml). The resulting reaction mixture was stirred for 4 hrs at room temperature. Solvent was then removed under reduced pressure. The crude salt was dissolved in ethyl acetate and washed with 1M aq. Na<sub>2</sub>CO<sub>3</sub> and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered and the solvent removed *in vacuo* to provide the title compound (230 mg, 92%). <sup>1</sup>H-NMR; δ (CDCl<sub>3</sub>), 7.51-7.44 (1H, dd, J = 8.73, 4.73 Hz), 7.28-7.21 (1H, m), 7.02-6.93 (1H, m), 4.05 (1H, s), 1.04 (9H, s).

**Step D: 4-Benzyloxy-2R-cyclopentylmethyl-N-[1S-(6-fluoro-1H-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-4-formylamino-butyramide**

To a solution of the 4-benzyloxy-2R-cyclopentylmethyl-4-formylamino-butyric acid pentafluorophenyl ester (426 mg, 9.05 mmol) in dichloromethane (6 ml) was added 1S-(6-fluoro-1H-benzoimidazol-2-yl)-2,2-dimethyl-propylamine (from Step C) (220 mg, 1.00 mmol), followed by triethylamine (189 µl, 1.36 mmol). The resulting reaction mixture was stirred for 12 hrs at room temperature. The reaction mixture was diluted with dichloromethane and washed with water (20 ml), 1M aq. Na<sub>2</sub>CO<sub>3</sub> and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered and the solvent was removed *in vacuo*. The residual yellow solid was purified by flash chromatography (hexanes/ethyl acetate from 1:2 to 1:5) to provide the title compound (270 mg, 59%).

**Step E: 2R-Cyclopentylmethyl-N-[1-(5-fluoro-1H-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-3-(formyl-hydroxy-amino)-propionamide**

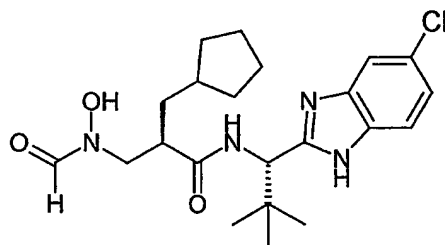
To a solution of 4-benzyloxy-2R-cyclopentylmethyl-N-[1S-(6-fluoro-1H-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-4-formylamino-butyramide (113 mg, 2.22 mmol) in ethanol (100 ml), under a blanket of argon, was added 10% palladium on charcoal (10 mg). Hydrogen was bubbled through the

suspension for 15 min and the reaction was stirred under an atmosphere of hydrogen for 15 min. The palladium catalyst was filtered off and the solvent was removed *in vacuo* to yield the title compound as a white foam (73 mg, 78%).  $^1\text{H-NMR}$ ;  $\delta$  ( $\text{CDCl}_3$ ), 8.41 (0.4H, br s), 7.94 (0.6H, br s), 7.60-7.09 (2H, m), 6.91 (1H, m), 6.43 (1H, m), 5.31 (0.5H, d), 5.16 (0.5H, d), 4.08 (0.5H, m), 3.93 (0.5H, m), 3.75 (0.5H, m), 3.58 (0.5H, m), 3.25 (0.5H, m), 3.02 (0.5H, m), 1.80-0.80 (11H, m), 1.02 (9H, s). HPLC data: RT 4.93 min.

The compounds of Examples 2-3 and 5-8 were prepared by analogy with Example 1 starting from the appropriate 1,2 diaminobenzene. The compound of Example 4 was prepared in a similar manner using 2*R*-[(benzoyloxy-formylamino)-methyl]-hexanoic acid in place of 4-benzyloxy-2*R*-cyclopentylmethyl-4-formylaminobutyric acid pentafluorophenyl ester.

### Example 2

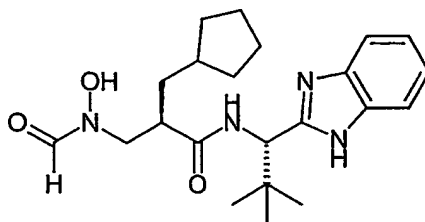
*N*-[1-(5-Chloro-1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide



$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CDCl}_3$ ), 8.44 (0.4H, s), 7.95 (0.6H, s), 7.71-7.48 (1H, m), 7.30-7.02 (2H, m), 5.30 (0.5H, d,  $J=9\text{Hz}$ ), 5.14 (0.5H, br s), 4.01-3.89 (1H, m), 3.80 (0.5H, d,  $J=12\text{Hz}$ ), 3.60 (0.5H, d,  $J=12\text{Hz}$ ), 3.23 (0.4H, br s), 3.01 (0.6H, br s) and 1.85-0.80 (20H, m). HPLC data: RT 4.84 min. LRMS: +ve ion 435 [ $\text{M}+1$ ], -ve ion 433 [ $\text{M}-1$ ].

Example 3

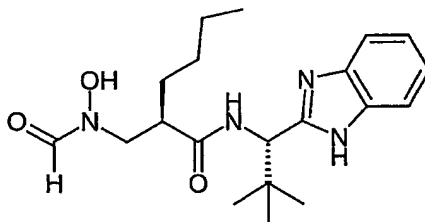
*N*-[1-(1*H*-Benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide



<sup>1</sup>H-NMR;  $\delta$  (CDCl<sub>3</sub>), 8.43 (0.5H, br s), 7.95 (0.5H, br s), 7.68 (1H, br s), 7.48-7.10 (4H, m), 5.39 (0.5H, d, J=9.6Hz), 5.26 (0.5H, d, J=8Hz), 4.11 (0.5H, m), 3.98-3.94 (0.5H, dd, J=10.8, 13.3Hz), 3.72 (0.5H, m), 3.59 (0.5H, d, J=11.8Hz), 3.26 (0.5H, br s), 3.04 (0.5H, br s) and 1.73-0.81 (20H, m). HPLC data: RT 4.42 min.

Example 4

2-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1-(1*H*-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-amide

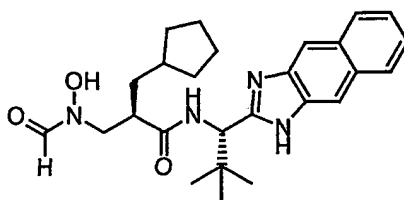


<sup>1</sup>H-NMR;  $\delta$  (CD<sub>3</sub>OD), 8.28 (0.3H, s), 7.85 (0.7H, s), 7.54 (2H, br s), 7.22 (2H, dd, J=6.1, 3.1Hz), 5.09 (0.7H, s), 5.07 (0.3H, s), 3.84-3.78 (0.3H, m), 3.79 (0.7H, dd, J=14.2, 9.5Hz), 3.63 (0.3H, dd, J=14.0, 5.5Hz), 3.44 (0.7H, dd, J=14.2, 4.6Hz), 3.17-2.97 (0.7H, m), 2.88-2.82 (0.3H, m), 1.58-1.35 (2H, m),

1.23-1.02 (4H, m), 1.04 (2.7H, s), 1.02 (6.3H, s), 0.65 (0.9H, t,  $J=6.8\text{Hz}$ ) and 0.63 (2.1H, t,  $J=7.1\text{Hz}$ ).

#### Example 5

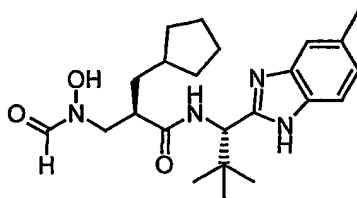
2R-Cyclopentylmethyl-N-[2,2-dimethyl-1S-(1H-naphtho[2,3-d]imidazol-2-yl)-propyl]-3-(formyl-hydroxy-amino)-propionamide



$^1\text{H-NMR}$ ;  $\delta$  (DMSO), 10.06 (0.4 H, s), 9.53 (0.6H, s), 8.30 (1.3H, m), 8.12 (1H, s), 7.97 (2H, d,  $J=9.3\text{Hz}$ ), 7.94 (1H, s), 7.81 (0.7H, s), 7.35 (2H, br s), 5.10 (1H, m), 3.63 (1H, m), 3.47 (0.6H, m), 3.32 (0.4H, m), 2.94 (1H, m), 1.67 (1H, m), 1.36 (2H, m), 1.08 (2H, m) 0.99 (9H, s) and 0.87 (2H, m).  $^{13}\text{C-NMR}$ ;  $\delta$  (DMSO), 173.4, 158.7, 158.5, 144.1, 134.7, 130.2, 129.7, 128.3, 127.7, 123.9, 123.2, 115.1, 106.8, 56.1, 52.5, 49.1, 43.2, 43.0, 37.9, 37.7, 36.1, 35.5, 32.6, 32.4, 32.3, 27.0 and 24.7. LCMS: +ve ion 451  $[\text{M}+\text{H}]$ , for major peak. HPLC: RT=3.54 min.

#### Example 6

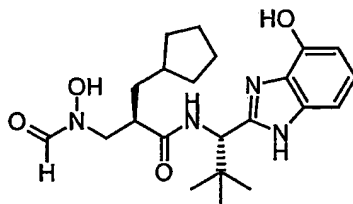
2R-Cyclopentylmethyl-N-[2,2-dimethyl-1S-(5-methyl-1H-benzoimidazol-2-yl)-propyl]-3-(formyl-hydroxy-amino)-propionamide



$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 8.29 (0.3H, s), 7.85 (0.7H, s), 7.41 (1H, d,  $J=8.1\text{Hz}$ ), 7.32 (1H, s), 7.05 (1H, d,  $J=8.2\text{Hz}$ ), 5.08 (1H, m), 3.80 (1H, m), 3.62 (0.3H, m), 3.44 (0.7H, m), 3.05 (0.7H, m), 2.91 (0.3H, m), 2.44 (3H, s), 1.41 (9H, m), 1.04 (3H, s), 1.01 (6H, s), 0.93 (2H, m).  $^{13}\text{C-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 176.5, 176.2, 164.4, 159.7, 154.5, 154.3, 133.9, 125.5, 73.0, 70.3, 65.1, 58.4, 58.3, 54.3, 50.7, 45.9, 45.8, 39.6, 37.9, 37.8, 37.6, 37.1, 36.8, 34.2, 34.1, 34.0, 27.5, 26.3 and 22.1. LRMS: +ve ion 415  $[\text{M}+\text{H}]$ , 437  $[\text{M}+\text{Na}]$ . HPLC: RT=5.16 min

#### Example 7

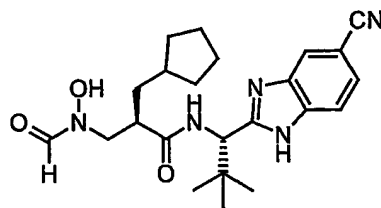
2R-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-N-[1S-(4-hydroxy-1H-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-propionamide



$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 8.28 (0.4H, s), 7.84 (0.6H, s), 7.01 (2H, m), 6.61 (1H, m), 5.09 (1H, m), 3.80 (1H, m), 3.62 (0.3H, m), 3.45 (0.7H, m), 2.87 (0.3H, m), 1.73 (1H, m), 1.38 (8H, m), 1.03 (3H, s), 1.01 (6H, s), 0.93 (2H, m).  $^{13}\text{C-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 176.4, 176.2, 164.3, 159.6, 153.2, 124.7, 108.4, 58.1, 54.3, 50.7, 46.0, 45.9, 39.7, 39.6, 37.9, 36.9, 34.1, 34.0, 27.5, 26.2 and 26.1. LRMS: +ve ion 417  $[\text{M}+\text{H}]$ , 439  $[\text{M}+\text{Na}]$ . HPLC: RT=4.62 min.

#### Example 8

N-[1S-(5-Cyano-1H-benzoimidazol-2-yl)-2,2-dimethyl-propyl]-2R-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

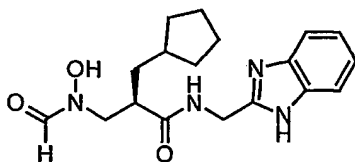


$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 8.29 (0.4H, s), 7.96 (1H, s), 7.86 (1H, d,  $J=8.3$  Hz), 7.54 (1H, d,  $J=8.3$  Hz), 5.11 (1H, m), 3.80 (1H, m), 3.61 (0.4H, m), 3.46 (0.6H, m), 3.10 (0.6H, m), 2.90 (0.4H, m), 1.41 (11H, m), 1.06 (3H, s) and 1.04 (6H, s).  $^{13}\text{C-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 176.8, 176.5, 164.4, 159.7, 158.7, 158.5, 127.4, 121.1, 106.7, 58.7, 58.4, 54.2, 50.7, 48.0, 45.6, 39.6, 37.9, 37.8, 36.6, 35.2, 34.5, 34.1, 34.0, 27.7, 27.4, 26.5, 26.2 and 18.8. LRMS: +ve ion 426  $[\text{M}+\text{H}]$ , -ve ion 424  $[\text{M}-\text{H}]$ . HPLC: RT=5.29 min.

Examples 9 & 10 were prepared by analogy with Example 1 using glycine in place of *t*-leucine.

#### Example 9

*N*-(1H-Benzimidazol-2-ylmethyl)-2R-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide

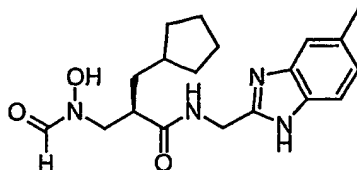


$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 8.32 (0.5 H, s), 7.89 (0.5H, s), 7.54 (2H, m), 7.22 (2H, m), 4.85 (1H, m), 4.42 (1H, m), 3.96 (0.1H, dd,  $J=13.9$  4.3 Hz), 3.83 (0.4H, dd,  $J=13.8$ , 4.8 Hz), 3.69 (1H, m), 3.56 (0.5H, dd,  $J=14.1$ , 4.8 Hz), 2.93 (0.5H, m), 2.80 (0.5H, m), 1.61 (9H, m) and 1.11 (2H, m).  $^{13}\text{C-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 177.5, 177.0, 164.6, 160.4, 153.7, 153.3, 124.1, 116.3, 116.1, 54.2, 53.8, 51.8, 46.5, 46.2, 46.0, 39.7, 39.6, 38.6, 38.3, 38.2, 37.7, 37.5, 34.4, 33.9, 33.8, 26.4 and 20.9. LRMS: +ve ion 345  $[\text{M}+\text{H}]$ , 367  $[\text{M}+\text{Na}]$ . HPLC: RT=4.72 min.



## Example 10

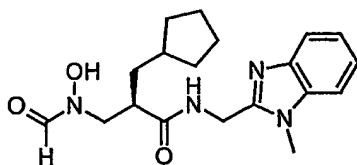
2R-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-*N*-(5-methyl-1H-benzimidazol-2-ylmethyl)-propionamide



$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 8.31 (0.5H, s), 7.89 (0.5H, s), 7.36 (2H, m), 7.04 (1H, d,  $J=7.9$  Hz), 4.80 (1H, m), 4.39 (1H, m), 3.69 (2H, m), 2.92 (0.5H, m), 2.80 (0.5H, m), 2.43 (3H, s), 1.60 (9H, m) and 1.13 (2H, m).  $^{13}\text{C-NMR}$ ;  $\delta$  ( $\text{CH}_3\text{OD}$ ), 177.4, 164.6, 153.3, 125.5, 54.1, 51.8, 46.2, 46.0, 39.6, 38.5, 38.3, 37.7, 34.5, 34.4, 33.9, 33.8, 26.4 and 22.0. LRMS: +ve ion 359 [M+H], -ve ion 357 [M-1].

## Example 11

2R-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-*N*-(1-methyl-1H-benzimidazol-2-ylmethyl)-propionamide



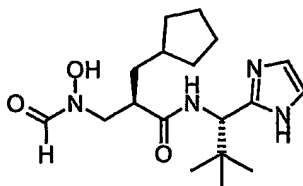
Example 11 was prepared in a similar manner to Example 1 using glycine in the place of *t*-leucine. The *N*-methyl substituent was introduced on to the benzimidazole nitrogen using the procedure detailed below.

2R-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-N-(1-methyl-1H-benzoimidazol-2-ylmethyl)-propionamide

To a solution of *N*-(1H-Benzoimidazol-2-ylmethyl)-2R-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionamide (80mg, 0.23 mmol) in anhydrous THF (7ml) was added triethylamine (30 $\mu$ l, 0.22 mmol) and iodomethane (14 $\mu$ l, 0.22 mmol). The reaction was stirred at 30°C for approx. 3.5 hours. The material had not fully dissolved, so DMF was added and the reaction stirred for a further 2 hours at 30°C. LRMS analysis showed presence of starting material, more triethylamine (30 $\mu$ l, 0.22 mmol) and iodomethane (14 $\mu$ l, 0.22 mmol) were added and the reaction stirred at 30°C over night. The solvent was removed *in vacuo* and the residue was dissolved in DCM, washed with water, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* and the crude mixture was purified by preparative HPLC to obtain the title compound as a yellow oil. <sup>1</sup>H-NMR;  $\delta$  (CH<sub>3</sub>OD), 8.31 (0.4 H, s), 7.87 (0.6H, s), 7.58 (2H, m), 7.26 (2H, m), 4.89 (1H, m), 4.55 (1H, m), 3.82 (1.2H, s), 3.81 (1.8H, s), 3.66 (2H, m), 2.93 (0.4H, m), 2.82 (0.6H, m), 1.63 (9H, m) and 1.09 (2H, m). <sup>13</sup>C-NMR;  $\delta$  (CH<sub>3</sub>OD), 177.2, 176.7, 164.6, 166.2, 130.6, 130.2, 128.2, 124.6, 124.1, 124.0, 123.9, 120.0, 119.4, 111.4, 54.1, 51.7, 46.1, 45.9, 39.6, 38.8, 38.4, 37.9, 37.6, 37.2, 34.4, 33.9, 30.8, 30.6 and 26.4. LRMS: +ve ion 359 [M+H], 381 [M+Na]. HPLC: RT=4.81 min.

Example 12

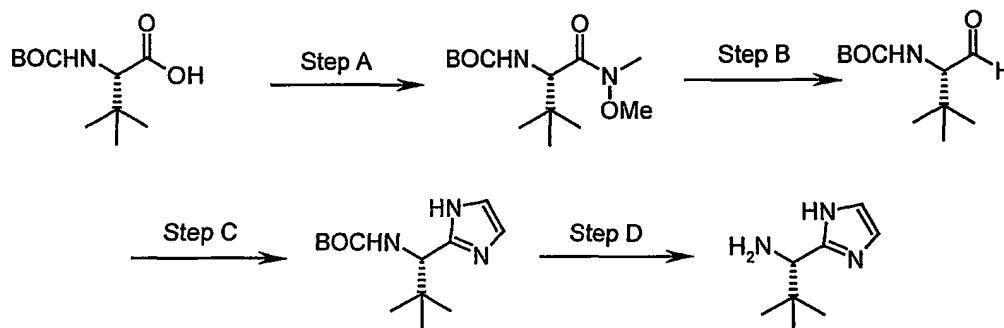
3-Cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-N-[1S-(1H-imidazol-2-yl)-2,2-dimethyl-propyl]-propionamide



$^1\text{H-NMR}$ ;  $\delta$  ( $\text{CDCl}_3$ ), 8.33 (0.6 H, s), 7.86 (0.4H, s), 7.81 (0.4H, s), 7.14 (0.6H, s), 6.90 (2H, m), 5.15 (0.4H, d,  $J=9.6\text{Hz}$ ), 5.06 (0.6H, d,  $J=8.6\text{Hz}$ ), 4.00 (0.6H, m), 3.88 (0.4H, m), 3.65 (0.6H, m), 3.47 (0.4H, m), 3.19 (0.4H, m), 2.98 (0.6H, m), 1.56 (9H, m), 0.96 (6H, m), 0.95 (2H, m) and 0.77 (3H, s). LRMS: +ve ion 351  $[\text{M}+\text{H}]$ , -ve ion 349  $[\text{M}-\text{H}]$ . HPLC:  $\text{RT}=3.37$  min.

The title compound was prepared from 2R-[(Benzyloxy-formylamino)-methyl]-hexanoic acid and 1S-(1H-imidazol-2-yl)-2,2-dimethyl-propylamine by analogy with Example 1. The preparation of 1S-(1H-imidazol-2-yl)-2,2-dimethyl-propylamine is detailed below (see Scheme 2)

Scheme 2



Step A: *N,N*-carbonyldiimidazole, *N,O*-dimethylhydroxylamine hydrochloride, DCM. Step B: 1M  $\text{LiAlH}_4$  in THF, anhydrous THF. Step C: 2M  $\text{NH}_3$  in MeOH, glyoxal trimer hydrate, MeOH. Step D: TFA, DCM.

Step A: [1S-(Methoxy-methyl-carbamoyl)-2,2-dimethyl-propyl]-carbamic acid *tert*-butyl ester

To a solution of BOC protected *t*-leucine (30g, 0.13 mol) in DCM (400ml) was added *N,N*-carbonyldiimidazole (63.3g, 0.39 mol) portionwise. Evolution of CO<sub>2</sub> gas was observed and the reaction allowed to stir for approx. 15 minutes before addition of *N,O*-dimethylhydroxylamine hydrochloride (38g, 0.39 mol). The reaction was stirred overnight at ambient temperature. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate, washed with 1M hydrochloric acid, saturated sodium carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to obtain a clear oil (26.5g) that was purified by flash chromatography (30% ethyl acetate/hexanes) when required.

<sup>1</sup>H-NMR;  $\delta$  (CH<sub>3</sub>OD) 5.20 (1H, br s), 4.67 (1H, d, J=9.5Hz), 3.79 (3H, s), 3.20 (3H, s), 1.44 (9H, s) and 0.99 (9H, s).

Step B: (1S-Formyl-2,2-dimethyl-propyl)-carbamic acid *tert*-butyl ester

To a stirred solution of [1S-(Methoxy-methyl-carbamoyl)-2,2-dimethyl-propyl]-carbamic acid *tert*-butyl ester (1.4g, 5.11 mmol) in anhydrous THF (40ml), under a blanket of argon and in a dry ice/acetone bath, was added lithium aluminium hydride. The reaction was stirred in the cooling bath for approx. 1 hour, then allowed to warm to room temperature and stir overnight. The reaction was cooled in an ice/water bath before addition of ethyl acetate (4ml), water (0.2ml), 2.5M sodium hydroxide (0.31ml) and water (0.5ml). The reaction mixture was allowed to warm to room temperature and stir for approx. 45 minutes. The resulting semi-solid was filtered off, washed with ethyl acetate and the filtrate concentrated *in vacuo* to obtain a pale yellow oil (1.02g, 92%). <sup>1</sup>H-NMR;  $\delta$  (CDCl<sub>3</sub>) 9.84 (1H, s), 5.15 (1H, br s), 4.15 (1H, br s), 1.44 (9H, s) and 1.04 (9H, s).

Step C: [1S-(1H-Imidazol-2-yl)-2,2-dimethyl-propyl]-carbamic acid *tert*-butyl

ester

To a stirred solution of (1S-Formyl-2,2-dimethyl-propyl)-carbamic acid tert-butyl ester (1.02g, 4.75 mmol) in methanol (6ml), was added 2M NH<sub>3</sub> in MeOH (11ml, 21.8 mmol) and glyoxal trimer hydrate (499mg, 2.37 mmol). The reaction was stirred at room temperature overnight, then diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to obtain a yellow oil (879mg) that was purified by flash chromatography (3-4% methanol/DCM) to yield a white solid (495mg, 95%). LRMS: +ve ion 254 [M+H], -ve ion 252 [M-1]. <sup>1</sup>H-NMR;  $\delta$  (CDCl<sub>3</sub>) 6.92 (2H, s), 5.70 (1H, d, J=9.8 Hz), 4.65 (1H, d, J=9.7 Hz), 1.42 (9H, s) and 0.99 (9H, s).

Step D: 1S-(1H-Imidazol-2-yl)-2,2-dimethyl-propylamine

To a solution of [1S-(1H-Imidazol-2-yl)-2,2-dimethyl-propyl]-carbamic acid tert-butyl ester (495mg, 1.95 mmol) in DCM (10ml), was added TFA (10ml). The reaction was stirred at room temperature for approx. 4 hours. The solvent was removed *in vacuo* and the TFA co-evaporated with toluene. The residue was dissolved in methanol and Amberlyst A-21 ion exchange resin was added until pH 8 was obtained. The resin was filtered off and the solvent removed *in vacuo* to obtain the title compound as an oil (276mg, 93%). LRMS: +ve ion 154 [M+H]. <sup>1</sup>H-NMR;  $\delta$  (CH<sub>3</sub>OD) 7.01 (2H, s), 3.85 (1H, s) and 0.96 (9H, s).

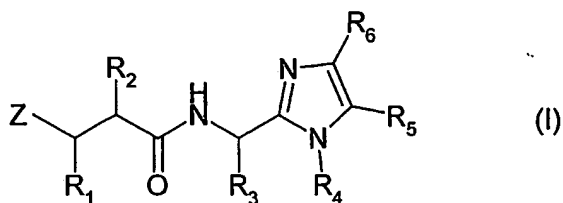
Biological Example

The susceptibilities of two strains of bacteria to the compounds of Example 1-4 were determined by a standard agar plate dilution method following recommendations in British Society for Antimicrobial Chemotherapy Working Party. 1991, "A guide to sensitivity testing British Society for Antimicrobial Chemotherapy, London, United Kingdom". Briefly, Iso-Sensitest agar (pH 7.2: Oxoid, United Kingdom) is employed, supplemented with 5% horse blood (Oxoid) and 20 µg of NAD (Sigma) per ml are added to support growth of fastidious bacteria. The inoculum used is approximately  $10^4$  colony forming units of each isolate contained in a volume of 1 µl. Plates are incubated 18 to 24 hr in air, or for fastidious bacteria an atmosphere enriched with 4-6% carbon dioxide at 35°C. The MIC is determined as the lowest concentration of an antimicrobial tested that inhibited growth of the inoculum, disregarding a single persisting colony or faint haze caused by the inoculation. The results were as follows:

| Example No | S. aureus ATCC 29213 | S. pneumoniae        |
|------------|----------------------|----------------------|
|            | MIC µg/ml            | ATCC 49619 MIC µg/ml |
| 1          | 4                    | 2                    |
| 2          | 8                    | 2                    |
| 3          | 8                    | 2                    |
| 4          | 8                    | 4                    |

## CLAIMS

1. The use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof in the preparation of a composition for treatment of bacterial or protozoal infections in humans and non-human mammals:



wherein:

Z represents a radical of formula  $-N(OH)CH(=O)$  or formula  $-C(=O)NH(OH)$ ;

$R_1$  represents hydrogen, methyl or trifluoromethyl, or, except when Z is a radical of formula  $-N(OH)CH(=O)$ , a hydroxy, halo or amino group;

$R_2$  represents a group  $R_{10}-(X)_n-(ALK)_m$  wherein

$R_{10}$  represents hydrogen, or a  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, cycloalkyl, aryl, or heterocyclyl group, any of which may be unsubstituted or substituted by  $(C_1$ - $C_6$ )alkyl,  $(C_1$ - $C_6$ )alkoxy, hydroxy, mercapto,  $(C_1$ - $C_6$ )alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, cyano, nitro, oxo,  $-COOH$ ,  $-CONH_2$ ,  $-COOR^A$ ,  $-NHCOR^A$ ,  $-CONHR^A$ ,  $-NHR^A$ ,  $-NR^A R^B$ , or  $-CONR^A R^B$  wherein  $R^A$  and  $R^B$  are independently a  $(C_1$ - $C_6$ )alkyl group and

ALK represents a straight or branched divalent  $C_1$ - $C_6$  alkylene,  $C_2$ - $C_6$  alkenylene, or  $C_2$ - $C_6$  alkynylene radical, and may be interrupted by one or more non-adjacent  $-NH-$ ,  $-O-$  or  $-S-$  linkages,

X represents -NH-, -O- or -S-, and

m and n are independently 0 or 1;

R<sub>3</sub> represents the side chain of a natural or non-natural alpha amino acid; and

R<sub>4</sub> represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl or phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl-; and

(a) R<sub>5</sub> and R<sub>6</sub> independently represent:

hydrogen, halogen, trifluoromethyl, or

(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, aryl, heterocyclyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl-, or heterocyclyl(C<sub>1</sub>-C<sub>6</sub>)alkyl-, any of which may be optionally substituted by

(C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, trifluoromethyl, cyano, nitro, oxo,

phenoxy or phenylthio-,

-OR<sup>A</sup>, -SR<sup>A</sup>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, -NHCOR<sup>A</sup> -CONHR<sup>A</sup>, -CONR<sup>A</sup>R<sup>B</sup>,  
or -COOR<sup>A</sup>, wherein

R<sup>A</sup> and R<sup>B</sup> are independently hydrogen or (C<sub>1</sub>-C<sub>4</sub>)alkyl,

or in the case where R<sup>A</sup> and R<sup>B</sup> are attached to a nitrogen atom then R<sup>A</sup> and R<sup>B</sup> taken together with the nitrogen atom to which they are attached form a monocyclic 5-7 membered ring; or

(b) R<sub>5</sub> and R<sub>6</sub> taken together with the carbon atoms to which they are attached form a fused monocyclic or bicyclic carbocyclic or heterocyclic ring which



may be further substituted with any of the substituent groups listed under (a).

2. A method for the treatment of bacterial or protozoal infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially or antiprotozoally effective dose of a compound of formula (I) as defined in claim 1.
3. A compound of formula (I) as set forth in claim 1 wherein Z is a radical of formula  $-N(OH)CH(=O)$ , or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof.
4. A compound of formula (I) as set forth in claim 1 wherein Z is a radical of formula  $-C(=O)NH(OH)$ , or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof.
5. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $R_1$  is hydrogen.
6. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $R_2$  is:
  - optionally substituted  $C_1$ - $C_8$  alkyl,  $C_3$ - $C_6$  alkenyl,  $C_3$ - $C_6$  alkynyl or cycloalkyl;
  - phenyl( $C_1$ - $C_6$  alkyl)-, phenyl( $C_3$ - $C_6$  alkenyl)- or phenyl( $C_3$ - $C_6$  alkynyl)- optionally substituted in the phenyl ring;
  - cycloalkyl( $C_1$ - $C_6$  alkyl)-, cycloalkyl( $C_3$ - $C_6$  alkenyl)- or cycloalkyl( $C_3$ - $C_6$  alkynyl)- optionally substituted in the cycloalkyl ring;
  - heterocyclyl( $C_1$ - $C_6$  alkyl)-, heterocyclyl( $C_3$ - $C_6$  alkenyl)- or heterocyclyl( $C_3$ - $C_6$  alkynyl)- optionally substituted in the heterocyclyl ring; or

$\text{CH}_3(\text{CH}_2)_p\text{O}(\text{CH}_2)_q-$  or  $\text{CH}_3(\text{CH}_2)_p\text{S}(\text{CH}_2)_q-$ , wherein  $p$  is 0, 1, 2 or 3 and  $q$  is 1, 2 or 3.

7. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $\text{R}_2$  is methyl, ethyl, *n*- or iso-propyl, *n*- and iso-butyl, *n*-pentyl, iso-pentyl, 3-methyl-but-1-yl, *n*-hexyl, *n*-heptyl, *n*-acetyl, *n*-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, or 4-methoxybenzyl.

8. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $\text{R}_2$  is *n*-propyl, *n*-butyl, *n*-pentyl, or cyclopentylmethyl.

9. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $\text{R}_3$  is:

the characterising group of a natural  $\alpha$ -amino acid, for example benzyl, or 4-methoxyphenylmethyl, in which any functional group may be protected, any amino group may be acylated and any carboxyl group present may be amidated; or

a group  $-\text{[Alk]}_n\text{R}_9$  where Alk is a  $(\text{C}_1\text{-C}_6)$ alkylene or  $(\text{C}_2\text{-C}_6)$ alkenylene group optionally interrupted by one or more -O-, or -S- atoms or - $\text{N}(\text{R}_{12})$ - groups [where  $\text{R}_{12}$  is a hydrogen atom or a  $(\text{C}_1\text{-C}_6)$ alkyl group],  $n$  is 0 or 1, and  $\text{R}_9$  is hydrogen or an optionally substituted phenyl, aryl, heterocyclyl, cycloalkyl or cycloalkenyl group or (only when  $n$  is 1)  $\text{R}_9$

may additionally be hydroxy, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, amino, halo, trifluoromethyl, nitro, -COOH, -CONH<sub>2</sub>, -COOR<sup>A</sup>, -NHCOR<sup>A</sup>, -CONHR<sup>A</sup>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, or -CONR<sup>A</sup>R<sup>B</sup> wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>)alkyl group; or

a benzyl group substituted in the phenyl ring by a group of formula -OCH<sub>2</sub>COR<sub>8</sub> where R<sub>8</sub> is hydroxyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, di((C<sub>1</sub>-C<sub>6</sub>)alkyl)amino, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkylamino; or

a heterocyclic(C<sub>1</sub>-C<sub>6</sub>)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, trifluoromethyl (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy, formyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, di-(C<sub>1</sub>-C<sub>6</sub>)alkylamino, mercapto, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, mercapto(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkylphenylmethyl; or

a group -CR<sub>a</sub>R<sub>b</sub>R<sub>c</sub> in which:

each of R<sub>a</sub>, R<sub>b</sub> and R<sub>c</sub> is independently hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl; or

R<sub>c</sub> is hydrogen and R<sub>a</sub> and R<sub>b</sub> are independently phenyl or heteroaryl such as pyridyl; or

R<sub>c</sub> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, or (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, and R<sub>a</sub> and R<sub>b</sub> together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R<sub>a</sub>, R<sub>b</sub> and R<sub>c</sub> together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

$R_a$  and  $R_b$  are each independently (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, phenyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, or a group as defined for  $R_c$  below other than hydrogen, or  $R_a$  and  $R_b$  together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and  $R_c$  is hydrogen, -OH, -SH, halogen, -CN, -CO<sub>2</sub>H, (C<sub>1</sub>-C<sub>4</sub>)perfluoroalkyl, -CH<sub>2</sub>OH, -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -O(C<sub>1</sub>-C<sub>6</sub>)alkyl, -O(C<sub>2</sub>-C<sub>6</sub>)alkenyl, -S(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -S(C<sub>2</sub>-C<sub>6</sub>)alkenyl, -SO(C<sub>2</sub>-C<sub>6</sub>)alkenyl, -SO<sub>2</sub>(C<sub>2</sub>-C<sub>6</sub>)alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO<sub>2</sub>- and W represents a phenyl, phenylalkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkylalkyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO<sub>2</sub>H, -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -CONH<sub>2</sub>, -CONH(C<sub>1</sub>-C<sub>6</sub>)alkyl, -CONH(C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>, -CHO, -CH<sub>2</sub>OH, (C<sub>1</sub>-C<sub>4</sub>)perfluoroalkyl, -O(C<sub>1</sub>-C<sub>6</sub>)alkyl, -S(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO(C<sub>1</sub>-C<sub>6</sub>)alkyl, -SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub>)alkyl, -N((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>, -NHCO(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>4</sub>-C<sub>8</sub>)cycloalkenyl, phenyl or benzyl.

10. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $R_3$  is methyl, ethyl, benzyl, 4-chlorobenzyl, 4-hydroxybenzyl, phenyl, cyclohexyl, cyclohexylmethyl, pyridin-3-ylmethyl, tert-butoxymethyl, naphthylmethyl, isobutyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, 1-methoxy-1-methylethyl, 1-hydroxy-1-methylethyl, 1-fluoro-1-methylethyl, hydroxymethyl, 2-hydroxyethyl, 2-carboxyethyl, 2-methylcarbamoyl, 2-carbamoyl, or 4-aminobutyl.

11. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $R_3$  is tert-butyl.

12. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $R_4$  is hydrogen or methyl.
13. A use as claimed in claim 1, a method as claimed in claim 2, or compound as claimed in claim 3 or claim 4 wherein  $R_5$  and  $R_6$  are independently hydrogen, methyl, trifluoromethyl, phenyl, bromo, chloro, fluoro, methoxy, hydroxymethyl, dimethylaminomethyl-, ethoxymethyl-, 4-methyl-piperazine-1-carbonyl-, 4-methyl-piperazin-1-ylmethyl-, morpholin-4-ylmethyl-, methoxycarbonyl, thiazol-2-yl-, phenoxymethyl-, pyrrolidin-1-ylmethyl-, piperidin-1-ylmethyl-,  $-C(O)NH_2$ ,  $(CH_2)_2CO_2CH_3$ ,  $-CH(OH)CH(CH_3)_2$ ,  $-CH(OH)CH_3$ , or  $-CH(OH)Ph$ ; or wherein  $R_5$  and  $R_6$  taken together with the carbon atoms to which they are attached form a fused benzo, naphtho or pyrido, for example a [4,5-c]pyridin-2-yl, ring, which may be substituted as specified, for example a fused benzo ring substituted by methyl, cyano, hydroxy, chloro or fluoro in the 4- or 5-position.
14. A compound as claimed in claim 14 wherein  $R_1$  is hydrogen,  $R_2$  is n-propyl, n-butyl, n-pentyl, or cyclopentylmethyl,  $R_3$  is tert-butyl, and  $R_4$  is hydrogen or methyl.
15. A compound of formula 1 as defined in claim 1 which is specifically named herein, or a pharmaceutically or veterinarily acceptable salt hydrate or solvate thereof.
16. A pharmaceutical composition comprising a compound as claimed in any of claims 3 to 14 together with a pharmaceutically acceptable carrier.

## INTERNATIONAL SEARCH REPORT

PCT/GB 01/04965

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 7 A61K31/16 A61K31/415 C07C259/04 C07D235/14 C07D233/54<br>A61P31/04 A61P33/02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                           |                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                           |                                                    |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 A61K                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                           |                                                    |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                           |                                                    |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)<br>EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                           |                                                    |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                           |                                                    |
| Category *                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                        | Relevant to claim No.                              |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | WO 96 33176 A (DU PONT MERCK PHARMA)<br>24 October 1996 (1996-10-24)<br>table 1<br>page 69, line 1-16 and page 72, line 10-23<br>---                                                                      | 1,4-7,<br>9-13,16                                  |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | WO 95 23790 A (SMITHKLINE BEECHAM CORP<br>;FRAZEE JAMES SIMPSON (US); GLEASON JOHN<br>G) 8 September 1995 (1995-09-08)<br>page 8, compound 5 and page 9, compound 7<br>page 21, line 16-20<br>---<br>-/-- | 4-7,12,<br>13,16                                   |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                           |                                                    |
| * Special categories of cited documents :<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier document but published on or after the international filing date<br>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.<br>"&" document member of the same patent family |                                                                                                                                                                                                           |                                                    |
| Date of the actual completion of the international search                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                           | Date of mailing of the international search report |
| 26 February 2002                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                           | 06/03/2002                                         |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                           | Authorized officer<br>Borst, M                     |

## INTERNATIONAL SEARCH REPORT

PCT/GB 01/04965

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                |                       |
|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category *                                           | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                             | Relevant to claim No. |
| X                                                    | CHEN J J ET AL: "Design, synthesis, activity, and structure of a novel class of matrix metalloproteinase inhibitors containing a heterocyclic P2'-P3' amide bond isostere"<br>BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB,<br>vol. 6, no. 13, 9 July 1996 (1996-07-09), pages 1601-1606, XP004175762<br>ISSN: 0960-894X<br>tables 1,2 | 4-7,9-13              |
| X                                                    | WO 99 59568 A (BRITISH BIOTECH PHARM ;HUNTER MICHAEL GEORGE (GB); SPAVOLD ZOE MAR) 25 November 1999 (1999-11-25)<br>page 2, last paragraph - page 6, paragraph 1                                                                                                                                                                               | 1,4-14, 16            |
| X                                                    | WO 99 39704 A (BRITISH BIOTECH PHARM ;DAVIES STEPHEN JOHN (GB); HUNTER MICHAEL GE) 12 August 1999 (1999-08-12)<br>cited in the application<br>page 2, last paragraph - page 6, paragraph 4                                                                                                                                                     | 1,3, 5-14,16          |
| X                                                    | WO 00 61134 A (BRITISH BIOTECH PHARM ;SMITH HELEN KATHERINE (GB); BECKETT RAYMOND) 19 October 2000 (2000-10-19)<br>cited in the application<br>page 2, last paragraph - page 8, paragraph 3                                                                                                                                                    | 1,3-14, 16            |

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01 04965

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 15

Present independent claim 15 relies to the description of the specification in respect of all its technical features. The scope of the claim is so unclear that meaningful search is not possible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



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